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<p>(54) Title: METHOD OF PREPARING 3-HALOALKYL-1H-PYRAZOLES</p> <p>(57) Abstract</p> <p>An efficient synthesis of 3-haloalkyl-1H-pyrazoles, suitable for adoption in a safe, large-scale process, has been developed.</p> <p style="text-align: right;">72</p>		

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METHOD OF PREPARING 3-HALOALKYL-1H-PYRAZOLES

Background

5 Pyrazoles have been widely described as
pharmaceutical therapeutic agents, including
antiinflammatories, and antidiabetic agents, among
others. More recently, [3-haloalkyl-1H-pyrazole-1-
yl]benzenesulfonamide have been identified as potent
10 antiinflammatories without the side effects commonly-
associated with such antiinflammatory agents. It became
apparent that there was no known method to prepare such
compounds, especially in a commercially viable one-pot
synthesis incorporating common starting materials and
15 reagents.

The formation of halogenated 1-aryl-butane-1,3-
diones has been described [K. Joshi et al., *Pharmazie*,
34, 68-9 (1979); K. Joshi et al., *J. Ind. Chem. Soc.*,
20 60, 1074-6 (1983); R. Yo and S. Livingstone, *Aust. J.*
Chem., 21, 1781-7 (1968); CA 2,041,134, ZA 7,104,221 and
DE 2,429,674].

In addition, the preparation of pyrazoles from the
25 condensation of diketones and hydrazines has been
described [EP 418,845, EP 554,829, T. Nishiwaki, *Bull.*
Chem. Soc. Japan, 42, 3024-26 (1969); J. Wright et al.,
J. Med. Chem., 7, 102-5 (1963); and R. Soliman and H.
Feid-Allah, *J. Pharm. Sci.*, 70, 602-5 (1980)].

30 However, these preparations do not provide a
scaleable commercial process. In addition, they require
isolation of the intermediate diketone, which adds to
the cost and complexity of the synthesis.

35

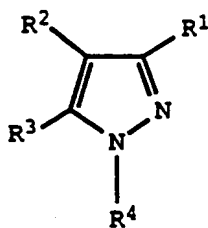
Summary of Invention

A scaleable procedure for the preparation of 1,3,4,5-substituted pyrazoles has not been previously described. Such pyrazoles have been indicated as having pharmaceutical activity including hypoglycemic activity and antiinflammatory activity.

This invention provides an efficient synthesis of 3-haloalkyl-1H-pyrazoles, suitable for adoption in a safe, large-scale process, and particularly for a one-pot synthesis.

Detailed Description of the Invention

This invention relates to a method of preparing 3-haloalkyl-1H-pyrazoles comprising the steps of forming a 4-halo-phenyl-butane-1,3-dione (or the keto-enol tautomer thereof) and treating said dione with a benzenesulfonamide to form the [3-haloalkyl-1H-pyrazol-1-yl]benzenesulfonamide. Specifically, the invention relates to a method of forming antiinflammatory compounds of Formula I



I

wherein R^1 is haloalkyl;
 wherein R^2 is selected from selected from hydrido, alkyl, cyano, hydroxyalkyl, cycloalkyl, alkylsulfonyl and halo;
 wherein R^3 is selected from cycloalkyl, cycloalkenyl, aryl and heteroaryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio,

cyano, nitro, haloalkyl, alkyl, hydroxyl, alkenyl, hydroxyalkyl, carboxyl, cycloalkyl, alkylamino, dialkylamino, alkoxycarbonyl, aminocarbonyl, alkoxy, haloalkoxy, heterocyclo and amino; and

- 5 wherein R⁴ is aryl substituted at a substitutable position with aminosulfonyl;

- the method comprising the steps of forming a 4-halo-1-phenyl-butane-1,3-dione by treating a ketone with a base
10 and a haloalkyl ester, and forming the 3-haloalkyl-1H-pyrazoles by treating said dione with an appropriate aryl hydrazine, or a salt thereof.

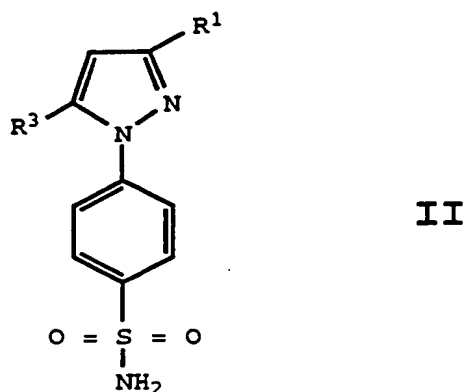
- Preferably, R¹ is lower haloalkyl; R² is selected
15 from hydrido, lower alkyl, cyano, lower hydroxyalkyl, lower cycloalkyl, lower alkylsulfonyl and halo; R³ is selected from lower cycloalkyl, lower cycloalkenyl, aryl and lower heteroaryl, wherein R³ is optionally substituted at a substitutable position with one or more
20 radicals selected from halo, cyano, nitro, hydroxyl, carboxyl, cycloalkyl, aminocarbonyl, lower alkylthio, lower alkyl, lower alkenyl, lower alkoxycarbonyl, lower haloalkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, lower N-alkylamino, lower N,N-dialkylamino,
25 5- or 6-membered heterocyclo and amino; and R⁴ is aryl substituted at a substitutable position with aminosulfonyl.

- More preferably, R¹ is selected from fluoromethyl,
30 difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, and dichloropropyl; wherein R² is
35 selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, hexyl, cyano, fluoro, chloro, bromo, methylsulfonyl, ethylsulfonyl, cyclopropyl, cyclopentyl,

cyclobutyl, hydroxypropyl, hydroxymethyl, and hydroxypropyl; wherein R^3 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, 4-cyclopentenyl, benzofuryl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydronaphthyl, benzothienyl, indenyl, indanyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, hexyl, ethenyl, propenyl, methylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, bromodifluoromethyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, aminosulfonyl, hydroxypropyl, hydroxyisopropyl, hydroxymethyl, hydroxyethyl, trifluoromethoxy, amino, N-methylamino, N-ethylamino, N-ethyl-N-methylamino, N,N-dimethylamino, N,N-diethylamino, piperidinyl, piperazinyl, morpholino, cyclohexyl, cyclopropyl, cyclobutyl, and nitro; and wherein R^4 is phenyl substituted at a substitutable position with aminosulfonyl; or a pharmaceutically acceptable salt thereof.

35

More specifically, the invention relates to a method of preparing compounds of Formula II



the method comprising forming a diketone of Formula III

5



by treating a ketone with a base and $R^1\overset{\text{O}}{\parallel}{C}-OR^5$, and
 10 treating the diketone with a 4-
 (aminosulfonyl)phenylhydrazine or a salt thereof, in a
 suitable solvent;

wherein R^1 is haloalkyl; wherein R^3 is selected
 from cycloalkyl, cycloalkenyl, aryl and heteroaryl;
 15 wherein R^3 is optionally substituted at a substitutable
 position with one or more radicals selected from halo,
 alkylthio, alkylsulfonyl, cyano, nitro, haloalkyl,
 alkyl, hydroxyl, alkenyl, hydroxyalkyl, carboxyl,
 cycloalkyl, alkylamino, dialkylamino, alkoxy carbonyl,
 20 aminocarbonyl, alkoxy, haloalkoxy, aminosulfonyl,
 heterocyclo and amino; and wherein R^5 is lower alkyl.

Preferably, compounds of Formula II can be
 prepared wherein R^1 is selected from lower haloalkyl;
 25 wherein R^3 is selected from lower cycloalkyl, lower
 cycloalkenyl, aryl and 5- or 6-membered heteroaryl;
 wherein R^3 is optionally substituted at a substitutable
 position with one or more radicals selected from halo,

cyano, nitro, hydroxyl, carboxyl, cycloalkyl, aminocarbonyl, aminosulfonyl, lower alkylthio, lower alkyl, lower alkenyl, lower alkylsulfonyl, lower alkoxycarbonyl, lower haloalkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, lower N-alkylamino, lower N,N-dialkylamino, 5- or 6-membered heterocyclo and amino; and wherein R⁵ is lower alkyl.

More preferably, the method can be used to prepare compounds wherein R¹ is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, and dichloropropyl; wherein R³ is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, 4-cyclopentenyl, benzofuryl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydronaphthyl, benzothieryl, indenyl, indanyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R³ is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, hexyl, ethenyl, propenyl, methylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, bromodifluoromethyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy,

ethoxy, propoxy, n-butoxy, aminosulfonyl, hydroxypropyl, hydroxyisopropyl, hydroxymethyl, hydroxyethyl, trifluoromethoxy, amino, N-methylamino, N-ethylamino, N-ethyl-N-methylamino, N,N-dimethylamino, N,N-diethylamino, piperidinyl, piperazinyl, morpholino, cyclohexyl, cyclopropyl, cyclobutyl, and nitro; and wherein R⁵ is selected from methyl and ethyl.

More preferably, the method can be used to prepare compounds wherein R¹ is selected from trifluoromethyl, difluoromethyl, pentafluoroethyl and heptafluoropropyl; wherein R³ is phenyl optionally substituted at a substitutable position with one or more substituents selected from fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, methylthio and hydroxyl.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH₂-) radical. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "alkylsulfonyl", it embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of such radicals include ethenyl, n-propenyl, butenyl, and the like. The term "halo" means halogens

such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are

5 monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of

10 different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloromethyl, pentafluoroethyl,

15 heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of

20 which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl,

25 hydroxypropyl, hydroxybutyl and hydroxyhexyl. The term "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms.

30 Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include

35 fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy. The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three

rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term

5 "heterocyclo" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered

10 heteromonocyclic group containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.];

15 saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and

20 dihydrothiazole. The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic group containing 1 to 4

25 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl,

30 etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-

35 b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur

atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. More preferred examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl. The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals -SO₂-.

"Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The term "arylsulfonyl" embraces aryl radicals as defined

above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl. The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such as "N-alkylaminosulfonyl", "N-arylamino-
5 sulfonyl", "N,N-dialkylaminosulfonyl" and "N-alkyl-N-arylamino-
sulfonyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide (-SO₂NH₂). The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl",
10 denotes -CO₂H. The terms "alkanoyl" or "carboxyalkyl" embrace radicals having a carboxy radical as defined above, attached to an alkyl radical. The alkanoyl radicals may be substituted or unsubstituted, such as formyl, acetyl, propionyl (propanoyl), butanoyl
15 (butyryl), isobutanoyl (isobutyryl), valeryl (pentanoyl), isovaleryl, pivaloyl, hexanoyl or the like. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes -(C=O)-. The term "alkylcarbonyl" embraces radicals having a carbonyl
20 radical substituted with an alkyl radical. More preferred alkylcarbonyl radicals are "lower alkylcarbonyl" radicals having one to six carbon atoms. Examples of such radicals include methylcarbonyl and ethylcarbonyl. The term "alkylcarbonylalkyl", denotes
25 an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" embraces alkoxy radicals having
30 one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "aminocarbonyl" when used by itself or with
35 other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylamino-
carbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylamino-
carbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-

hydroxyaminocarbonylalkyl", denotes an amide group of the formula $-C(=O)NH_2$. The term "aminoalkyl" embraces alkyl radicals substituted with amino radicals. The term "alkylaminoalkyl" embraces aminoalkyl radicals having the nitrogen atom substituted with an alkyl radical. The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkenyl" embraces unsaturated cyclic radicals having three to ten carbon atoms, such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3-S-) . The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent $-S(=O)-$ atom. The terms "N-alkylamino" and "N,N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. More preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "alkylamino" may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes

amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term

5 "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals, such as N-benzylamino. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from

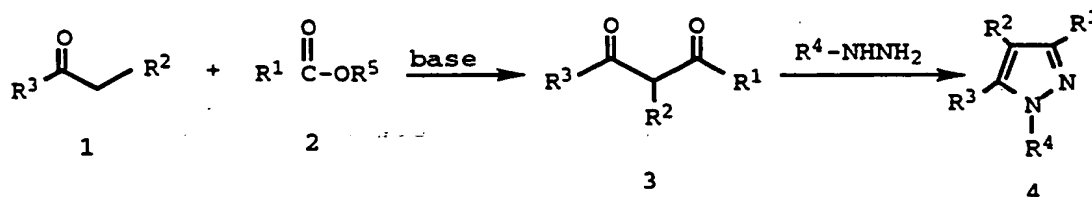
10 an organic acid. The term "ester" includes alkylated carboxylic acids or their equivalents, such as (RCO-imidazole).

GENERAL SYNTHETIC PROCEDURES

15 A general Scheme for the preparation of antiinflammatory pyrazoles of Formulas I-II are shown in the following Schemes where R¹-R⁵ are as previously defined.

20

Scheme I



Synthetic Scheme I shows the two steps of the

25 present method. In step one, the diketone 3 is formed, such as by treatment of ketone 1 with base and ester 2 in a suitable solvent. In step 2, the diketone 3 is condensed with the hydrazine to form pyrazole 4.

30 Suitable bases include alkali metal alcoholates and alkaline earth metal alcoholates. Examples of alkali metal alcoholates include lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium

propoxide, sodium propoxide, potassium propoxide, lithium isopropoxide, sodium isopropoxide, potassium isopropoxide, lithium butoxide, sodium butoxide, potassium butoxide, lithium isobutoxide, sodium isobutoxide, potassium isobutoxide, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium pentoxide, sodium pentoxide, and potassium pentoxide. Examples of alkaline earth metal alkoxides include calcium dimethoxide, magnesium dimethoxide, calcium diethoxide, magnesium diethoxide, calcium dipropoxide, magnesium dipropoxide, calcium di(isopropoxide), magnesium di(isopropoxide), calcium dibutoxide, magnesium dibutoxide, calcium di(isobutoxide), and magnesium di(isobutoxide).

15

Preferably, alkali metal alcoholates are used, and more preferably, sodium methoxide.

Suitable solvents include organic solvents which are inert under the reaction conditions, ethers, aliphatic or aromatic hydrocarbons, cyclic or linear amides and alcohols, for example. Examples of such ethers include diethyl ether, diisopropyl ether, dibutyl ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, dioxane, tetrahydrofuran, tetrahydropyran and methyl tert-butyl ether (MTBE). Cyclic ethers and higher molecular weight linear ethers are preferred, and MTBE is more preferred. Mixtures of these solvents may also be used. Examples of such hydrocarbons include pentane, hexane, heptane, petroleum ethers, benzene, toluene and xylene. An example of a cyclic or linear amide is N-methyl-pyrrolidone. Examples of such alcohols include ethanol and isopropanol.

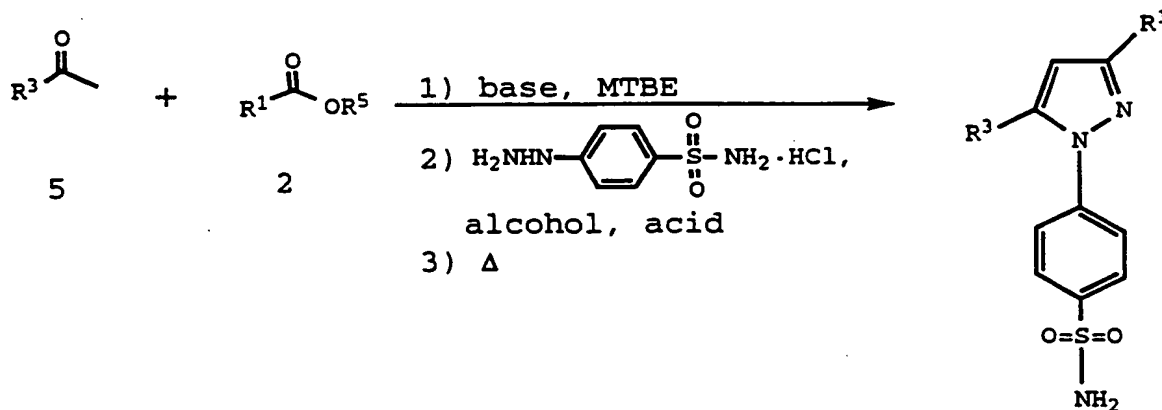
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Excess amounts of the reagents, specifically the ester and aryl hydrazine can be used, although equimolar amounts are preferred.

5 The reaction takes place at relatively low reaction temperatures. For example, the diketone can be formed at a temperature range of about 15 to about 70 °C. Preferably it is formed at a temperature of about 20 to about 60 °C. The pyrazole is preferably
10 formed at reflux temperature. More preferably, it is formed at a temperature of about 50 to about 60 °C.

 Preferably, the pH of the reaction mixture is below 7 before the hydrazine is added. More
15 preferably, aqueous HCl is added before the hydrazine is added.

Scheme II



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6

Synthetic Scheme II shows a method of forming 4-[3-haloalkyl-1H-pyrazol-1-yl]benzenesulfonamides. In step one, the diketone 3 is formed, such as by
25 treatment of ketone 5 with base and ester 2 in a suitable solvent. The diketone 3 is condensed, without

isolation or further purification, with the hydrazine to form pyrazole 6.

Suitable bases include alkali metal alcoholates.

- 5 Examples of alkali metal alcoholates include lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, and lithium propoxide. Preferably, sodium methoxide is used.

10

- Suitable solvents for the diketone formation step include organic solvents which are inert under the reaction conditions, ethers, for example. Examples of such ethers include diethyl ether, diisopropyl ether, 15 dibutyl ether, ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, dioxane, tetrahydrofuran, tetrahydropyran and methyl *tert*-butyl ether (MTBE). Cyclic ethers and higher molecular weight linear ethers are preferred, and MTBE is more 20 preferred. Mixtures of these solvents may also be used. Suitable solvents for the pyrazole-forming step include aqueous-miscible solvents, such as alcohols and organic acids. Examples of such alcohols include ethanol and isopropanol.

25

Excess amounts of the reagents, specifically the ester and aryl hydrazine can be used, although equimolar amounts are preferred.

30

The reaction takes place at relatively low reaction temperatures. For example, the diketone can be formed at a temperature range of about 15 to about 70 °C. Preferably it is formed at a temperature of about 20 to about 60 °C. The pyrazole is preferably 35 formed at reflux temperature. More preferably, it is formed at a temperature of about 50 to about 60 °C.

Preferably, the pH of the reaction mixture is below 7 before the hydrazine is added. More preferably, aqueous HCl is added before the hydrazine is added.

5

A further advantage of the present process is that materials can be carried through the above steps without purification of the intermediate compounds. However, if purification is desired, the intermediates disclosed can be isolated.

The following examples contain detailed descriptions of the methods of preparation of pyrazoles of Formulas I-II. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated.

Example 1

25 **4-[5-(4-Methylphenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide**

To a solution of ethyl trifluoroacetate (1.90 ml, 16.0 mmol) in 7 ml of MTBE was added 25% NaOMe (3.62 ml, 16.8 mmol). Next 4'-chloroacetophenone (2.08 ml, 16.0 mmol) in 2 ml of MTBE was added. The mixture was stirred at room temperature overnight. To above solution was added 100 ml of 90% EtOH, followed by 4N HCl (4.0 ml, 16 mmol) and 4-sulphonamidophenylhydrazine hydrochloride (3.58 g, 16 mmol). The mixture was heated to reflux for 3 hours. The mixture was concentrated. When 30 ml of water was added, a solid formed. The solid was filtered and washed with 20 ml

of 60% EtOH to give 4.50 g of white solid. The filtrate was evaporated and taken up in ethyl acetate (100 ml), washed with sat. NaHCO₃, and brine, dried over MgSO₄, and concentrated. Heptane was added at boiling point of the mixture. After cooling down to 0 °C, 1.01 g more product was obtained. The combined yield of the first two crops was 86%.

Example 2

4-[5-(3-Fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide

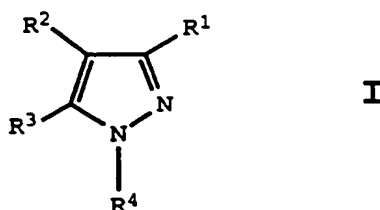
To a solution of 4'-methoxy-3'-fluoroacetophenone (21.5 g, 128 mmol) in 137 ml of methyl t-butyl ether (MTBE) was added ethyl difluoroacetate (16.6 ml, 166 mmol) at 25 °C. Sodium methoxide (25 wt%) in methanol (35.0 ml, 154 mmol) was added. The mixture was heated to reflux for 3 hours (pot temperature reached to 54 °C in 15 minutes). Prepare a slurry of 4-sulphonamidophenylhydrazine hydrochloride (28.6 g, 128 mmol) in 200 ml of EtOH. To above solution was added water (246 ml), 37% HCl (12.8 ml, 154 mmol) and 4-sulphonamidophenylhydrazine hydrochloride (3.58 g, 16 mmol) in 200 ml EtOH. The mixture was heated to reflux for 3 hours (pot temperature reached 62 °C). The solution was cooled to 5±5 °C to precipitate the product which was filtered and washed with water. The product was recrystallized from ethyl acetate and water to give a white solid (39.95 g, mp 162-163 °C).

From the foregoing detailed description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is Claimed is:

1. A method of preparing [3-haloalkyl-1H-pyrazol-1-yl]benzenesulfonamides comprising the steps of forming a 1-aryl-4-halobutane-1,3-dione and treating said dione with a aminosulfonylphenyl hydrazine, or salt thereof, to form the [3-haloalkyl-1H-pyrazol-1-yl]benzenesulfonamide.

2. A method of preparing compounds of Formula I



wherein R^1 is haloalkyl;

wherein R^2 is selected from selected from hydrido, alkyl, cyano, hydroxyalkyl, cycloalkyl, alkylsulfonyl and halo;

wherein R^3 is selected from cycloalkyl, cycloalkenyl, aryl and heteroaryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, cyano, nitro, haloalkyl, alkyl, hydroxyl, alkenyl, hydroxyalkyl, carboxyl, cycloalkyl, alkylamino, dialkylamino, alkoxy carbonyl, aminocarbonyl, alkoxy, haloalkoxy, heterocyclo and amino; and

wherein R^4 is aryl substituted at a substitutable position with aminosulfonyl;

the method comprising the steps of forming a 4-halo-1-phenyl-butane-1,3-dione by treating a ketone with a base and a haloalkyl ester, and forming the 3-haloalkyl-1H-pyrazoles by treating said dione with an appropriate aryl hydrazine, or a salt thereof.

3. The method of Claim 2 wherein R^1 is lower haloalkyl; wherein R^2 is selected from hydrido, lower alkyl, cyano, lower hydroxyalkyl, lower cycloalkyl, lower alkylsulfonyl and halo; wherein R^3 is selected from lower cycloalkyl, lower cycloalkenyl, aryl and lower heteroaryl, wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from halo, cyano, nitro, hydroxyl, carboxyl, cycloalkyl, aminocarbonyl, lower alkylthio, lower alkyl, lower alkenyl, lower alkoxy, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, lower N-alkylamino, lower N,N-dialkylamino, 5- or 6-membered heterocyclo and amino; and wherein R^4 is aryl substituted at a substitutable position with aminosulfonyl.

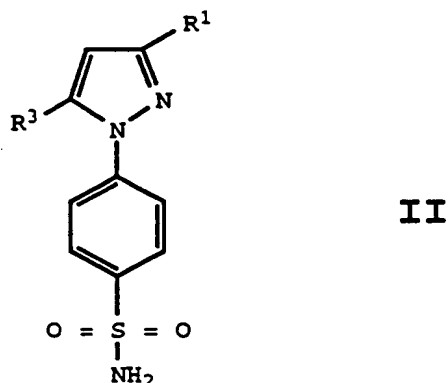
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4. The method of Claim 3 wherein R^1 is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, and dichloropropyl; wherein R^2 is selected from hydrido, methyl, ethyl, isopropyl, tert-butyl, isobutyl, hexyl, cyano, fluoro, chloro, bromo, methylsulfonyl, ethylsulfonyl, cyclopropyl, cyclopentyl, cyclobutyl, hydroxypropyl, hydroxymethyl, and hydroxypropyl; wherein R^3 is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, 4-cyclopentenyl, benzofuryl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydronaphthyl, benzothienyl, indenyl, indanyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methyl,

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ethyl, propyl, isopropyl, *tert*-butyl, isobutyl, hexyl, ethylenyl, propenyl, methylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, bromodifluoromethyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, *n*-butoxy, aminosulfonyl, hydroxypropyl, hydroxyisopropyl, hydroxymethyl, hydroxyethyl, trifluoromethoxy, amino, *N*-methylamino, *N*-ethylamino, *N*-ethyl-*N*-methylamino, *N,N*-dimethylamino, *N,N*-diethylamino, piperidinyl, piperazinyl, morpholino, cyclohexyl, cyclopropyl, cyclobutyl, and nitro; and wherein R⁴ is phenyl substituted at a substitutable position with aminosulfonyl.

20 5. A method of preparing compounds of Formula II



25 the method comprising forming a diketone of Formula III



by treating a ketone with a base and $R^1 \overset{\text{O}}{\parallel} C-OR^5$, and treating the diketone with a 4-(aminosulfonyl)phenylhydrazine or a salt thereof, in a suitable solvent;

5 wherein R^1 is haloalkyl; wherein R^3 is selected from cycloalkyl, cycloalkenyl, aryl and heteroaryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from halo, alkylthio, alkylsulfonyl, cyano, nitro, haloalkyl, alkyl, hydroxyl, 10 alkenyl, hydroxyalkyl, carboxyl, cycloalkyl, alkylamino, dialkylamino, alkoxycarbonyl, aminocarbonyl, alkoxy, haloalkoxy, aminosulfonyl, heterocyclo and amino; and wherein R^5 is lower alkyl.

15 6. The method of Claim 5 wherein the 4-aminosulfonylphenyl hydrazine is 4-(aminosulfonyl)phenylhydrazine, hydrochloride salt.

20 7. The method of Claim 5 wherein the haloalkylester is selected from ethyltrifluoroacetate, methyltrifluoroacetate, methyldifluoroacetate, ethyldifluoroacetate, ethyl pentafluoropropionate, ethyl heptafluorobutyrate, and methyl 2-chloro-2,2-difluoroacetate.

25 8. The method of Claim 5 wherein the base is an alkali metal alcoholate.

30 9. The method of Claim 8 wherein the base is sodium methoxide.

35 10. The method of Claim 5 wherein R^1 is lower haloalkyl; wherein R^3 is selected from lower cycloalkyl, lower cycloalkenyl, aryl and 5- or 6-membered heteroaryl; wherein R^3 is optionally substituted at a substitutable position with one or more radicals selected from halo,

cyano, nitro, hydroxyl, carboxyl, cycloalkyl, aminocarbonyl, lower alkylthio, lower alkyl, lower alkenyl, lower alkoxy carbonyl, lower haloalkyl, lower alkoxy, lower hydroxyalkyl, lower haloalkoxy, lower N-alkylamino, lower N,N-dialkylamino, 5- or 6-membered heterocyclo and amino; and wherein R⁵ is lower alkyl.

11. The method of Claim 10 wherein R¹ is selected from fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, and dichloropropyl; wherein R³ is selected from phenyl, naphthyl, biphenyl, cyclohexyl, cyclopentyl, cycloheptyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 4-cyclohexenyl, 1-cyclopentenyl, 4-cyclopentenyl, benzofuryl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydronaphthyl, benzothieryl, indenyl, indanyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl and pyrazinyl; wherein R³ is optionally substituted at a substitutable position with one or more radicals selected from fluoro, chloro, bromo, methylthio, methyl, ethyl, propyl, isopropyl, tert-butyl, isobutyl, hexyl, ethylenyl, propenyl, methylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, propoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, pentoxycarbonyl, aminocarbonyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, bromodifluoromethyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, hydroxyl, methoxy, methylenedioxy, ethoxy, propoxy, n-butoxy, hydroxypropyl, hydroxyisopropyl, hydroxymethyl, hydroxyethyl, trifluoromethoxy, amino, N-methylamino, N-

ethylamino, N-ethyl-N-methylamino, N,N-dimethylamino, N,N-diethylamino, piperidinyl, piperazinyl, morpholino, cyclohexyl, cyclopropyl, cyclobutyl, and nitro; and wherein R⁵ is selected from methyl and ethyl.

5

12. The method of Claim 11 wherein R¹ is selected from trifluoromethyl, difluoromethyl, pentafluoromethyl and heptafluoropropyl; and wherein R³ is phenyl optionally substituted at a substitutable position with one or more
10 substituents selected from fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, methylthio and hydroxyl.

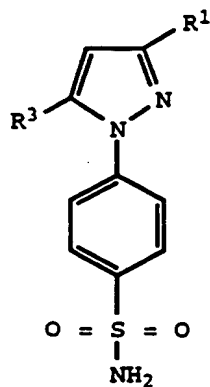
13. The method of Claim 12 wherein the compound is
15 4-[5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide.

14. The method of Claim 12 wherein the compound is
20 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide.

15. The method of Claim 5 wherein the solvent is a selected from ethers, alcohols and a mixture thereof.

16. The method of Claim 15 wherein the solvent is a
25 mixture of methyl tert-butyl ether and ethanol.

17. A method of preparing compounds of Formula II



II

wherein R¹ is selected from trifluoromethyl, difluoromethyl, pentafluoromethyl and heptafluoropropyl; and wherein R³ is phenyl optionally substituted at a substitutable position with one or more substituents selected from fluoro, chloro, bromo, methyl, ethyl, methoxy, ethoxy, methylthio and hydroxyl;

the method comprising the steps of mixing in methyl *tert*-butyl ether, a substituted acetophenone, an alkyl haloacetate and sodium methoxide, and treating the mixture with a solution of 4-(aminosulfonyl)phenyl hydrazine, or a salt thereof, in acidified ethanol.

18. The method of Claim 17 wherein the substituted acetophenone is selected from 4'-chloroacetophenone, 4-methylacetophenone, 3'-fluoro-4'-methoxyacetophenone and 4'-fluoroacetophenone.

INTERNATIONAL SEARCH REPORT

Initial Application No

PCT/US 96/07506

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 554 829 (FUJISAWA PHARMACEUTICAL CO) 11 August 1993 cited in the application see page 4; claim 8 ---	1-14
X	JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 70, no. 6, 1981, WASHINGTON US, pages 602-605, XP002011104 R. SOLIMAN; H.M. FEID-ALLAH: "Preparation and antidiabetic activity of new 3-methyl-5-phenylpyrazolesulfonylurea derivatives" cited in the application see experimental part and scheme I --- -/--	1-14

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

20 August 1996

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INTERNATIONAL SEARCH REPORT

Int: Application No
PCT/US 96/07506

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 15316 (SEARLE & CO ;TALLEY JOHN J (US); PENNING THOMAS D (US); COLLINS PA) 8 June 1995 see examples -----	1-14

INTERNATIONAL SEARCH REPORT

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PCT/US 96/07506

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		CA-A- 2088835	06-08-93
		CN-A- 1075959	08-09-93
		JP-A- 5246997	24-09-93
		ZA-A- 9300077	04-08-93

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		US-A- 5504215	02-04-96
